REMARKS / ARGUMENTS

In response to the Office Action, Applicant has amended claims 1, 5 and 8, and has canceled claims 2 to 4 and 11 to 13. Claims 6, 7, 9 and 10 have been maintained.

Claim rejections under 35 U.S.C. 112(a)

Claims 1 to 10 were rejected as being indefinite. Claim 1 has been amended to deal with all objections raised on this point. In particular, step (i) now refers to "said sensing device", for which antecedent can be found in the preamble. Step (ii) no longer refers to "the predetermined parameters", but refers simply to "parameters:", after which a list of six parameters is provided. In step (iii), the term "said measured parameters" has been deleted and replaced with the term "said parameters", for which antecedent can be found in step (ii).

Claim 4 has been canceled. However, the term "surrounding liquid medium" is introduced in the preamble of claim 1 as amended.

Claim 3 has been canceled. However, the subject matter previously recited in claim 3 has been included in the final paragraph of claim 1 beginning "wherein...".

Previous claims 11 to 13 have been cancelled to overcome the objection on the ground of indefiniteness.

Claim rejections under 35 U.S.C. 102(b)

Claims 11 to 13 were rejected on the ground that the subject matter was anticipated by Ferrante *et al.*, 1994. The Applicants respectfully disagree, but nevertheless have cancelled these claims without prejudice.

Claim rejections under 35 U.S.C. 103(a)

The Examiner rejected the subject matter of claims 1 to 10 as being unpatentably obvious over Cavic et al. (1997) in view of U.S. Patent No. 6,287,874 ('874) to Hefti; Ferrante et al. (1994) and U.S. Patent 6,060,023 ('023) to Maracas. Applicants have amended independent claim 1 to traverse this objection, in combination with the rationale put forth below.

Claim 1 has been amended to include the limitations previously recited in claims 2 to 4, as well as to provide clarifying wording. The steps involved in the claimed process for sensing a chemical change are now clearly set forth in independent claim 1. Claims 5 to 7 recite limitations relating to the nature of the biomolecule attached to the surface of the sensing device, while claims 8 to 10 recite limitations relating to the nature of the biological entity in the surrounding medium.

With Reference to the Counterpart European Application. Please note that the corresponding application EP 00963840.4 was allowed in Europe. The European Patent Office issued a Decision to Grant Communication under Rule 51(4) EPC. A copy of a related communication is enclosed, along with the claims to which the notice pertains. The Applicant decided not to proceed in Europe, and did not pay the fees to issue the application in Europe. The wording of the allowable claims in Europe is reflected in the amended claims now put forth in the instant application. In particular, amended claim 1 as now put forward reflects the combined wording of allowed European claims 1 and 2. Dependent claims 5 to 7 of the instant application reflect the subject matter of allowed European claim 3. Dependent claims 8 to 10 of the instant application reflect the subject matter of allowed European claim 4.

Support for the Amendments to Claim 1. Provided below are the passages of support for new claim 1, derived from the specification and claims of record.

• The phrase "a chemical change in molecular conformation or mass" is supported by claim 2 as originally filed, which uses the phrase "molecular conformation and/or molecular mass". This phrase is now used consistently in the claims. Similar terminology is also used on page 5 (line 14) and page 6 (line 30).

• The phrase "said change being attributable to a binding interaction between said biomolecule attached to the surface and a biological entity in a surrounding liquid medium upon exposure of the surface to the surrounding liquid medium" is supported by claim 4 (as originally filed), and by the exemplary biomolecules and biological entities noted in the specification, for example at pages 6 (lines 6 to 19) and in Example 1. The concept that the interaction is a binding interaction is supported by page 6 (line 14), page 7 (lines 8 and 21) and is supported by the binding referred to in the Example.

• That step i) includes exciting "prior to and during exposure to the surrounding liquid medium" is a mere clarification of the process, and is supported by the use of "real time" evaluation in a flow-through system, as exemplified in the Example at page 7 (line 18), and by

comparison of baseline and signal values at page 7 (lines 26 to 30) and page 8 (lines 1 and 2).

• That the relative change is determined "upon exposure of the surface to the surrounding liquid medium" in step iii) is supported by the Example, in which the flow through of the liquid represents exposure to the liquid medium.

• Step iv) is fully supported by claim 2 as originally filed, with the final wording of this step ("attributable to a binding interaction upon exposure to the surrounding liquid medium") reflecting the wording used earlier in the claim.

• The final paragraph of the claim beginning "wherein..." is fully supported by claim 3 as originally filed with some clarification of the terms. For example: "slip parameter (α)" has been clarified to recite "boundary layer slip parameter (α)", consistent with the term used earlier in the claim; and "molecular structural shape" has been amended to "molecular conformation", consistent with claim 2 as originally filed.

Rationale to Illustrate that the Claims are Not Obvious. Although the Examiner has objected to claims 1 to 10 under 35 U.S.C. 103(a) as being obvious in view of the combined teachings of the applied references, in no instance has the Examiner provided adequate factual support for a *prima facie* conclusion of obviousness. The Applicants herein provide rationale as to why the Examiner has failed to meet the burden of factual support for *prima facie* obviousness. Each document is discussed individually, followed by a summary of why it is believed that *prima facie* obviousness has not been established.

Cavic et al. (1997). The document of Faraday Discuss. 107: 159-176 (1997) employs a TSM sensor with surface-immobilized neutravidin to illustrate that binding is indicated when changes in series resonant frequency of the sensor are detected. However, there is no disclosure of collecting and determining changes in the other parameters noted in claim 1 step ii), in particular: motional resistance (Rm), motional inductance (Lm), motional capacitance (Cm), electrostatic capacitance (Co), and boundary layer slip parameter (α).

On page 174 of Cavic et al., there is brief mention of preliminary work that showed a drop in motional resistance. However, there is no indication of how a change in this parameter can be correlated or used in combination with other parameters to arrive at the subject matter now claimed in claim 1. Aside from this brief mention, parameters other than resonance frequency shift are not discussed or implied in this paper.

U.S. Patent No. 6,287,874 (Hefti). This document teaches a method for analyzing protein binding events at a molecular binding region on a circuit having transmission lines to provide propagation of a signal. The Applicants believe that this reference has been improperly applied, because it does not relate to the field of transverse shear piezoelectric sensing devices (or TSM). In fact, the substrates to which a molecule may be bound according to this reference include bio-assay devices outlined in columns 18 to 20. None of these devices is relevant to transverse shear piezoelectric sensing devices, as is described and claimed in the instant application. Although a number of parameters may be evaluated in detecting bound molecular structures in the '874 patent, nowhere in the document is it suggested or implied to evaluate the parameters of: series resonance frequency shift (fS), motional resistance (Rm), motional inductance (Lm), motional capacitance (Cm), electrostatic capacitance (Co), and boundary layer slip parameter (α). Each of these parameters is required in step ii) of claim 1 as amended.

The Applicants disagree with the Examiner's assertion that this reference teaches the measurement of frequency, resistance, inductance and capacitance to detect a molecular binding event. The Examiner has not indicated any relevant passage in which these parameters were combined, much less combined in a way that implies use in a process even remotely similar to that described in claim 1 as amended.

Ferrante et al. (1994). The document of J. Applied Physics 76/6 (1994) p 3448-3462 (Ferrante et al.) teaches the use of an impedance measurement to determine molecular slip at the interface of a bulk acoustic wave quartz chemical sensor and a liquid. The sensor coatings used included hydrophilic and hydrophobic chemical coatings, as opposed to biomolecules (see page 3349 under section "A. Sensor"). The liquid to which the sensor surface was exposed comprised water-glycerol solutions of varying concentrations (see page 3459 under section "E. Liquid"). In the ensuing experiments conducted in this reference, the surface of the sensor was contacted with the various aqueous glycerol solutions not due to changes in molecular conformation or mass of molecules at the sensor surface (as specified in the claims of the instant application), but instead are attributable to "attractive forces" between the surface and the glycerol solution (see page 3450, under "A. Interfacial slip parameter"). It is postulated that the alteration in attractive forces at the surface causes a change in transverse shear wave propagation. There is no suggestion in this document that ***binding*** of molecules in the liquid to analytes present on the surface would have a similar

effect. Nowhere does this document equate the effect of charge-based "attractive forces" with a binding interaction at the sensor surface.

Ferrante *et al.* teaches an "interfacial slip model", as described mathematically in the sections of the paper on pages 3459 and 3460 bearing this title. The document provides a model in which the "slip" between two masses (m1 and m2), one being a liquid particle moving past the sensor surface, the other a molecule on the surface of the sensor, can be calculated. This slip varies with the viscosity of the liquid. In the final conclusion of this paper, it is stated that this mechanical model of slip shows higher slip when the liquid in contact with the sensor surface is water, but lower slip when the liquid is more viscous than water (a combination of water and glycerol). The document does not disclose or imply that the interfacial slip model could be applied to a biological sensor. In fact, Ferrante *et al.* makes no mention of biomolecules, or sensing the presence of an unknown biomolecule within the fluid itself. The glycerol additive to the aqueous solution was used to adjust viscosity of the liquid, and the observations made were simply based on viscosity, not on binding. Interactions of the viscous liquid with the molecules on the sensor surface were limited to charge-based attraction, but did not include any type of binding, as is specified in the claims of the instant application. Such biological binding occurrences as hybridization, or antigen-antibody interaction as discussed in the instant application would be known to have a different effect than the simple attractive forces described in Ferrante *et al.*

As outlined specifically on page 3460 (column 2, lines 4 to 16) of Ferrante *et al.*, the interfacial slip parameter (α) is calculated as a function of displacement of a liquid particle and a solid particle at the sensor surface. The specification of the instant application addresses this specifically at page 3, lines 4 to 7, which state: "The viscous loading effect is also well known, however, in the current use of this effect, the transfer of acoustic energy at the surface is considered to be perfect, that is, there is no slip between the sensor surface and the adjacent fluid molecules". Later on page 3 (lines 26 to 28), it is explained that the effect of imposition or loss of material from a liquid medium, so as to change viscosity of the medium, will change motional resistance. This was not suggested or taught in Ferrante *et al.*, as only the viscosity was altered. Ferrante *et al.* does not teach or suggest a loss of material from a liquid medium through a binding interaction of that material with a biomolecule bound to the sensor surface. In the instant invention, a variety of parameters are specifically evaluated to indicate binding of a biological entity to a biomolecule. The resulting changes result in a loss

of material from the liquid medium (due to binding of the biological entity to the surface-attached biomolecule) and a change in viscosity. This was not taught or suggested in Ferrante *et al.*

U.S. Patent No. 6,060,023 (Maracas). This document describes an apparatus for use in molecular sensing. The substrate (reference number 14 of Figure 2 or number 80 of Figure 3) is not relevant to the field of transverse shear piezoelectric sensing devices. Nowhere in the document is there any suggestion that the substrate has properties relating to transverse shear piezoelectric material. Indeed, there is mention of terminology similar to that used in the instant application. The Applicants do not purport to be the first researchers ever to have measured electrical properties such as inductance, capacitance or impedance. However, it is the process in which these parameters are employed that sets the invention apart inventively from this and other applied references. The Examiner has failed to point out any mention in this document of a process remotely similar to that now claimed in amended claim 1. Again, the reference is poorly suited for combining with art related to transverse shear piezoelectric sensing devices.

In summary, the combination of teachings in the applied references would not allow one skilled in the art to conclude that evaluation of series resonance frequency shift (fS), motional resistance(Rm), motional inductance (Lm), motional capacitance (Cm), static capacitance (Co) and boundary layer slip parameter (α) would allow detection of a change in molecular conformation or mass of a biomolecule attached to a TSM sensor. Thus, the process as now described in claim 1 should be considered both novel and inventive.

No Case Has Been Established for prima facie Obviousness. The Applicants believe that the Examiner has not established a case of *prima facie* obviousness, and requests that the objection be withdrawn. According to MPEP 2143, the three basic criteria for establishing *prima facie* obviousness are 1) suggestion or motivation in the references themselves or generally that the references be modified to combine the teachings; 2) reasonable expectation of success; 3) a teaching or suggestion that the combination be made, and the expectation of success must both be found in the prior art (not in the Applicants' disclosure). These criteria are referred to herein as the first criterion, the second criterion, and the third criterion.

The first criterion for establishing *prima facie* obviousness has not been met. The prior art references do not provide suggestion or motivation (either within the references themselves or generally) that the teachings of the references be modified to arrive at the process steps now described. There is no motivation provided to combine transverse shear piezoelectric sensing device technology with other types of electrical sensors. Additionally, there is no motivation to combine the data from the parameters recited in step ii) of claim 1 as amended.

The second criterion for establishing *prima facie* obviousness has not been met, specifically, there was no reasonable expectation of success, taking into account any combination or modification of the cited references. Those working outside of the field of transverse shear piezoelectric sensing devices could not expect to be successful in application of unrelated technology to this field. The two applied patents are in unrelated fields, and a person skilled in the art would understand that transverse shear piezoelectric sensing devices are physically different devices than the "substrates" described in the applied patents. As such, success could not be expected. However, the references still do not combine to provide all of the aspects now provided in claim 1. Success would still be out of reach, because nowhere are the process steps adequately described in a way to allow successful application in a different substrate model.

The third criterion for establishing *prima facie* obviousness has not been met, in particular, there is no teaching or suggestion that a combination (or modification) be made. Nowhere is it suggested or taught in any reference or combination of references that these parameters be measured and used in the process now described in claim 1.

Claims 5 to 10 either directly or indirectly depend from claim 1 as amended. Thus, all of the arguments put forward with respect to claim 1 apply to these claims also, but are not reiterated here in the interests of brevity.

For the above reasons, the Applicants believe that the claims should now be considered inventive, and it is requested that the obviousness objections be withdrawn.

It is respectfully submitted that with this amendment, the Applicants have clarified the inventive features for the reader as well as distanced the claimed subject matter inventively

from the applied references. Withdrawal of the rejections in view of the amendments made is respectfully requested.

A fee for responding after expiry of the shortened 3-month statutory period is applicable for this submission.

The fee for a two-month extension of time is submitted herewith.

If any other fee is required, the Applicants authorize the Commissioner to debit any required fee from Deposit Account No. 501593, in the name of Borden Ladner Gervais LLP. The Commissioner is further authorized to debit any additional amount required, and to credit any overpayment to the above-noted deposit account.

Respectfully submitted,
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Enclosures:
1. Communication regarding Extension of Time for Decision to Grant under Rule 51(4) EPC
2. Allowed European Claims 1 to 4 from EP 00963840.4